



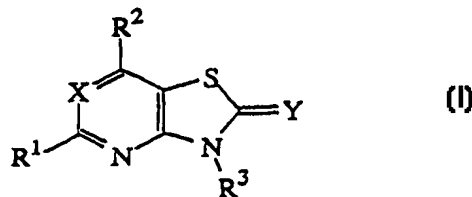
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| (51) International Patent Classification ⁶ : C07D 513/04, A61K 31/505, 31/44, 31/425 | A1 | (11) International Publication Number: WO 99/51608 (43) International Publication Date: 14 October 1999 (14.10.99) |
| (21) International Application Number: PCT/US99/06825 (22) International Filing Date: 29 March 1999 (29.03.99) (30) Priority Data: 60/080,537 3 April 1998 (03.04.98) US (71) Applicant: DU PONT PHARMACEUTICALS COMPANY [US/US]; WR-1ST18, 974 Centre Road, Wilmington, DE 19807 (US). (72) Inventor: BECK, James, Peter; 983 Tamara Drive, Smyrna, DE 19977 (US). (74) Agent: BROWDER, Monte, R.; Du Pont Pharmaceuticals Company, Legal Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US). | | (81) Designated States: AU, BR, CA, CN, CZ, EE, HU, IL, IN, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, UA, VN, ZA, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |

(54) Title: THIAZOLO[4,5-d]PYRIMIDINES AND PYRIDINES AS CORTICOTROPIN RELEASING FACTOR (CRF) ANTAGONISTS

(57) Abstract

The present invention describes novel thiazolo[4,5-d]pyrimidines of formula (I), or a pharmaceutically acceptable salt thereof, wherein X is CR⁴ or N; Y is selected from the group: S, O and NR⁵; R¹ is selected from the group: H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, Cl, F, Br, I, -CN, C₁₋₅ haloalkyl, -NR⁶R⁷, -NR⁶COR⁷, -OR⁸, -SH, and -S(O)_nR⁹; R² is selected from the group: -CR¹⁰R¹¹R¹², -NR^{10a}R^{11a}, -NHCR^{10R}R^{11R}R¹², -OCR^{10R}R^{11R}R¹², and phenyl, wherein the phenyl is substituted with 0-4 R^a; R³ is selected from the group: phenyl, pyridyl, pyrimidyl, naphthyl, triazinyl, furanyl, quinoliny, isoquinoliny, thienyl, thiazolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothieryl, benzothiazolyl, isoxazolyl, and pyrazolyl, and is substituted with 1 to 4 R^b groups; R⁴ is selected from the group: H, C₁₋₄ alkyl, and C₁₋₄ haloalkyl, halogen, NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkyl)₂, CN, OR⁸; and R⁵ is -CO(C₁₋₄ alkyl) or -CO₂(C₁₋₄ alkyl), which are useful as CRF antagonists.



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TITLE

THIAZOLO[4,5-d]PYRIMIDINES AND PYRIDINES AS CORTICOTROPIN
RELEASING FACTOR (CRF) ANTAGONISTS

5

FIELD OF THE INVENTION

This invention relates to novel thiazolo[4,5-d]
pyrimidines and pyridines, pharmaceutical compositions
containing the same and methods of using same in the treatment
10 of psychiatric disorders and neurological diseases including
affective disorder, anxiety, depression, headache, irritable
bowel syndrome, post-traumatic stress disorder, supranuclear
palsy, immune suppression, Alzheimer's disease,
gastrointestinal diseases, anorexia nervosa or other feeding
15 disorder, drug addiction, drug or alcohol withdrawal symptoms,
inflammatory diseases, cardiovascular or heart-related
diseases, fertility problems, human immunodeficiency virus
infections, hemorrhagic stress, obesity, infertility, head and
spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic
20 lateral sclerosis, hypoglycemia or a disorder the treatment of
which can be effected or facilitated by antagonizing CRF,
including but not limited to disorders induced or facilitated
by CRF.

25

BACKGROUND OF THE INVENTION

Corticotropin releasing factor (herein referred to as
CRF), a 41 amino acid peptide, is the primary physiological
regulator of proopiomelanocortin (POMC)-derived peptide
secretion from the anterior pituitary gland [J. Rivier et al.,
30 *Proc. Nat. Acad. Sci. (USA)* 80:4851 (1983); W. Vale et al.,
Science 213:1394 (1981)]. In addition to its endocrine role
at the pituitary gland, immunohistochemical localization of
CRF has demonstrated that the hormone has a broad
extrahypothalamic distribution in the central nervous system
35 and produces a wide spectrum of autonomic,
electrophysiological and behavioral effects consistent with a
neurotransmitter or neuromodulator role in brain [W. Vale et
al., *Rec. Prog. Horm. Res.* 39:245 (1983); G.F. Koob, *Persp.*

Behav. Med. 2:39 (1985); E.B. De Souza et al., *J. Neurosci.* 5:3189 (1985)]. There is also evidence that CRF plays a significant role in integrating the response of the immune system to physiological, psychological, and immunological stressors [J.E. Blalock, *Physiological Reviews* 69:1 (1989); J.E. Morley, *Life Sci.* 41:527 (1987)].

Clinical data provides evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and feeding disorders. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Parkinson's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis as they relate to the dysfunction of CRF neurons in the central nervous system [for review see E.B. De Souza, *Hosp. Practice* 23:59 (1988)].

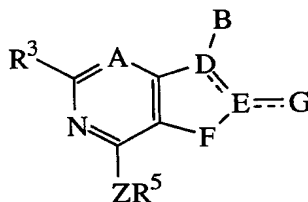
In affective disorder, or major depression, the concentration of CRF is significantly increased in the cerebral spinal fluid (CSF) of drug-free individuals [C.B. Nemeroff et al., *Science* 226:1342 (1984); C.M. Banki et al., *Am. J. Psychiatry* 144:873 (1987); R.D. France et al., *Biol. Psychiatry* 28:86 (1988); M. Arato et al., *Biol Psychiatry* 25:355 (1989)]. Furthermore, the density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C.B. Nemeroff et al., *Arch. Gen. Psychiatry* 45:577 (1988)]. In addition, there is a blunted adrenocorticotropin (ACTH) response to CRF (i.v. administered) observed in depressed patients [P.W. Gold et al., *Am J. Psychiatry* 141:619 (1984); F. Holsboer et al., *Psychoneuroendocrinology* 9:147 (1984); P.W. Gold et al., *New Eng. J. Med.* 314:1129 (1986)]. Preclinical studies in rats and non-human primates provide additional support for the hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R.M. Sapolsky, *Arch. Gen. Psychiatry* 46:1047 (1989)]. There is preliminary evidence that tricyclic antidepressants can alter CRF levels and thus modulate the numbers of CRF receptors in brain [Grigoriadis et al., *Neuropsychopharmacology* 2:53 (1989)].

There has also been a role postulated for CRF in the etiology of anxiety-related disorders. CRF produces anxiogenic effects in animals and interactions between benzodiazepine/non-benzodiazepine anxiolytics and CRF have been demonstrated in a variety of behavioral anxiety models [D.R. Britton et al., *Life Sci.* 31:363 (1982); C.W. Berridge and A.J. Dunn *Regul. Peptides* 16:83 (1986)]. Preliminary studies using the putative CRF receptor antagonist α -helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrate that the antagonist produces "anxiolytic-like" effects that are qualitatively similar to the benzodiazepines [C.W. Berridge and A.J. Dunn *Horm. Behav.* 21:393 (1987), *Brain Research Reviews* 15:71 (1990)]. Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics providing further evidence for the involvement of CRF in these disorders. Chlordiazepoxide attenuates the "anxiogenic" effects of CRF in both the conflict test [K.T. Britton et al., *Psychopharmacology* 86:170 (1985); K.T. Britton et al., *Psychopharmacology* 94:306 (1988)] and in the acoustic startle test [N.R. Swerdlow et al., *Psychopharmacology* 88:147 (1986)] in rats. The benzodiazepine receptor antagonist (Ro15-1788), which was without behavioral activity alone in the operant conflict test, reversed the effects of CRF in a dose-dependent manner while the benzodiazepine inverse agonist (FG7142) enhanced the actions of CRF [K.T. Britton et al., *Psychopharmacology* 94:306 (1988)].

The mechanisms and sites of action through which the standard anxiolytics and antidepressants produce their therapeutic effects remain to be elucidated. It has been hypothesized however, that they are involved in the suppression of the CRF hypersecretion that is observed in these disorders. Of particular interest is that preliminary studies examining the effects of a CRF receptor antagonist (α -helical CRF9-41) in a variety of behavioral paradigms have demonstrated that the CRF antagonist produces "anxiolytic-like" effects qualitatively similar to the benzodiazepines [for review see G.F. Koob and K.T. Britton,

In: *Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide*, E.B. De Souza and C.B. Nemeroff eds., CRC Press p221 (1990)].

5 EP 0,778,277 (EP '277) describes a variety of CRF antagonists including those of the formula:



10 wherein A can be N or C, D can be N or C, E can be N or C, G can be O, S, or N, and F can be O, S, N, or C. EP '277 does not disclose any thiazolo[4,5-d]pyrimidines and pyridines. Furthermore, group B is not considered part of the presently claimed compounds.

15 In view of the above, efficacious and specific antagonists of CRF are needed as potentially valuable therapeutic agents for the treatment of psychiatric disorders and neurological diseases. It is thus desirable to discover new CRF antagonists.

20 SUMMARY OF THE INVENTION

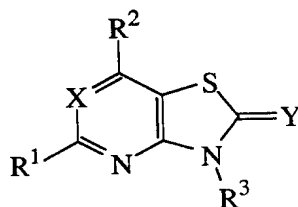
Accordingly, one object of the present invention is to provide novel thiazolo[4,5-d]pyrimidines and pyridines which are useful as CRF antagonists or pharmaceutically acceptable salts or prodrugs thereof.

25 It is another object of the present invention to provide pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt form thereof.

30 It is another object of the present invention to provide a method for treating psychiatric disorders and neurological diseases comprising administering to a host in need of such treatment a therapeutically effective amount of at least one

of the compounds of the present invention or a pharmaceutically acceptable salt form thereof.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of formula I:

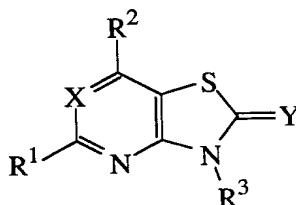


I

or pharmaceutically acceptable salt forms thereof, wherein R¹, R², R³, X and Y are defined below, are CRF antagonists.

DETAILED DESCRIPTION OF THE INVENTION

[1] Thus, in a first embodiment, the present invention provides a novel compound of the formula (I):



I

or a pharmaceutically acceptable salt thereof, wherein:

X is CR⁴ or N;

Y is selected from the group: S, O and NR⁵;

R¹ is selected from the group: H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, Cl, F, Br, I, -CN, C₁₋₅ haloalkyl, -NR⁶R⁷, -NR⁶COR⁷, -OR⁸, -SH, and -S(O)_nR⁹;

n is independently at each occurrence selected from the group: 0, 1, and 2;

R² is selected from the group: -CR¹⁰R¹¹R¹², -NR^{10a}R^{11a}, -NHCR¹⁰R¹¹R¹², -OCR¹⁰R¹¹R¹², and phenyl, wherein the phenyl is substituted with 0-4 R^a;

5 R^a is independently at each occurrence selected from the group: Cl, F, Br, I, C₁₋₄ haloalkyl, -NO₂, C₁₋₄ alkyl, C₂₋₅ alkenyl, C₂₋₄ alkynyl, C₃₋₇ cycloalkyl, C₂₋₅ carboalkoxy, SH, -S(C₁₋₄ alkyl), -CN, -OH, C₁₋₄ alkoxy, and -NR⁶R⁷, OR⁸, COR⁷;

10

R³ is selected from the group: phenyl, pyridyl, pyrimidyl, naphthyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, thiazolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, isoxazolyl, and pyrazolyl,
15 and is substituted with 1 to 4 R^b groups;

20

R^b is independently at each occurrence selected from the group: C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, (C₃₋₈ cycloalkyl)C₁₋₄ alkyl-, NO₂, Cl, F, Br, I, -CN, C₁₋₆ haloalkyl, -NR¹⁴R¹⁵, -NR⁸COR¹⁴, -NR⁸CO₂R¹⁴, -COR¹⁴, -OR¹⁴, -CONR¹⁴R¹⁵, -CO₂R¹⁴, -SH, and -S(O)_nR¹⁴;

25

R⁴ is selected from the group: H, C₁₋₄ alkyl, and C₁₋₄ haloalkyl, halogen, NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkyl)₂, CN, OR⁸;

R⁵ is -CO(C₁₋₄ alkyl) or -CO₂(C₁₋₄ alkyl);

30

R⁶ and R⁷ independently at each occurrence selected from the group: H, C₁₋₄ alkyl, and C₃₋₆ cycloalkyl;

35

R⁸ is independently at each occurrence selected from the group: H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, and C₃₋₆ cycloalkyl;

R⁹ is independently at each occurrence selected from the group: C₁₋₄ alkyl, C₁₋₄ haloalkyl, and aryl;

5 R^{10} and R^{11} are independently at each occurrence selected from the group: C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, $(C_{3-8}$ cycloalkyl) C_{1-4} alkyl-, $-(CH_2)_n$ aryl, $-(CH_2)_n$ heteroaryl, $(C_{1-6}$ alkoxy) C_{1-6} alkyl-, $-C_{0-6}-CN$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl) $_2$, and (carbo- C_{1-6} alkoxy) C_{0-6} alkyl-, each R^{10} and R^{11} being optionally substituted with 0-3 R^C ;

10 R^C is independently at each occurrence selected from the group: F, =O, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, $-CN$, $S(O)_n C_{1-4}$ alkyl, NH_2 , $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl) $_2$, phenyl, pyridyl, and pyrimidyl;

15 R^{12} is independently at each occurrence selected from the group: H, C_{1-6} alkyl;

20 alternatively, R^{10} and R^{11} are taken together, along with the interconnected carbon, to form a 4-8 membered saturated or partially saturated carbocyclic ring substituted with 0-2 R^e or a 4-8 membered saturated or partially saturated heterocyclic ring containing 1-2 heteroatoms selected from O, N, NR^8 , and S and substituted with 0-2 R^d ;

25 R^d is independently at each occurrence selected from the group: =O, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, $-CN$, $-S(O)_n C_{1-4}$ alkyl, $-NH_2$, $-NH(C_{1-4}$ alkyl), $-N(C_{1-4}$ alkyl) $_2$, and phenyl;

30 R^{10a} and R^{11a} are independently at each occurrence selected from the group: C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(C_{3-8}$ cycloalkyl) C_{1-4} alkyl-, $-(CH_2)_n$ aryl, $-(CH_2)_n$ heteroaryl, $(C_{1-6}$ alkoxy) C_{1-6} alkyl-, $-C_{1-6}-CN$, $-NH(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl) $_2$, (carbo- C_{1-6} alkoxy) C_{1-6} alkyl-, $S(O)_n R^8$, $C(O)_{1-2} R^8$, and $C(O)NR^6 R^7$ each R^{10a} being substituted with 0-3 R^C ;

35

alternatively, R^{10a} and R^{11a} are taken together, along with the interconnected nitrogen, to form a 4-8 membered saturated or partially saturated heterocyclic ring containing 0-1 additional heteroatoms selected from O, N, NR⁸, and S and substituted with 0-3 R^e;

R¹⁴ and R¹⁵ are independently at each occurrence selected from the group: H, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₃-C₆ cycloalkyl, (C₃-8 cycloalkyl)C₁-4 alkyl-, aryl, -(C₁-C₄ alkyl)aryl, heteroaryl and -(C₁-C₄)heteroaryl;

aryl is phenyl substituted with 0-3 R^e;

R^e is independently selected at each occurrence from the group: C₁-4 alkyl, C₂-4 alkenyl, C₂-5 alkynyl, C₃-6 cycloalkyl, -NO₂, Cl, F, Br, I, -CN, C₁-4 haloalkyl, -NH₂, -NH(C₁-4 alkyl), -N(C₁-4 alkyl)₂, OR¹⁴, S(O)_nR¹⁴; and,

heteroaryl is independently at each occurrence selected from the group: pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl and pyrazolyl substituted with 0-3 R^f.

[2] In a preferred embodiment, the present invention provides novel compounds, wherein:

Y is S or O;

R¹ is selected from the group: H, C₁-4 alkyl, C₂-4 alkenyl, C₂-4 alkynyl, Cl, F, -CN, C₁-5 haloalkyl, and -NR⁶R⁷;

R³ is selected from the group: phenyl, pyridyl, and pyrimidyl, and is substituted with 1 to 4 R^b groups;

R^b is independently at each occurrence selected from the group: C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₃₋₆ cycloalkyl, (C₃₋₈ cycloalkyl)C₁₋₄ alkyl-, NO₂, Cl, F, -CN, C₁₋₄ haloalkyl, -NR¹⁴R¹⁵, -NR⁸COR¹⁴, -NR⁸CO₂R¹⁴, -COR¹⁴, -OR¹⁴, -CONR¹⁴R¹⁵, -CO₂R¹⁴, -SH, and -S(O)_nR¹⁴;

heteroaryl is independently at each occurrence selected from the group: pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, imidazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, isoxazolyl and pyrazolyl substituted with 0-3 R^e.

[3] In a more preferred embodiment, the present invention provides a compound selected from the group:

3-(2-Bromo-4-isopropyl)phenyl-5-methyl-7-morpholino-thiazolo[4,5-d]pyrimidin-2-thione;

3-(2-Bromo-4-isopropyl)phenyl-7-(N-cyclopropylmethyl-N-propyl)amino-5-methylthiazolo[4,5-d]pyrimidin-2-thione;

3-(2-Bromo-4-isopropyl)phenyl-7-(N,N-diethylamino)-5-methylthiazolo[4,5-d]pyrimidin-2-thione;

7-(N,N-bismethoxyethylamino)-3-(2-bromo-4-isopropyl)phenyl-5-methylthiazolo[4,5-d]pyrimidin-2-thione;

3-(2-Bromo-4-isopropyl)phenyl-7-(N-butyl-N-ethyl)amino-5-methylthiazolo[4,5-d]pyrimidin-2-thione;

3-(2-Bromo-4-isopropyl)phenyl-7-(N,N-di-sec-butylamine)-5-methylthiazolo[4,5-d]pyrimidin-2-thione;

7-(N,N-diethylamino)-5-methyl-3-(2,4,6-trimethyl)phenylthiazolo[4,5-d]pyrimidin-2-thione;

- 7- (N,N-bismethoxyethylamino)-5-methyl-3-(2,4,6-trimethyl)phenylthiazolo[4,5-d]pyrimidin-2-thione;
- 5 7- (N-cyclopropylmethyl-N-propyl)-5-methyl-3-(2,4,6-trimethyl)phenylthiazole[4,5-d]pyrimidin-2-thione;
- 3-(2-Bromo-4-isopropyl)phenyl-7- (N-cyclopropylmethyl-N-propyl) amino-5-methylthiazolo[4,5-d]pyrimidin-2-one;
- 10 7- (N,N-bismethoxyethylamino)-3-(2-bromo-4-isopropyl)phenyl-5-methylthiazolo[4,5-d]pyrimidin-2-one;
- 3-(2-Bromo-4-isopropyl)phenyl-7- (N,N-diethylamino)-5-methylthiazolo[4,5-d]pyrimidin-2-one;
- 15 7- (N,N-diethylamino)-5-methyl-3-(2,4,6-trimethyl)phenylthiazolo[4,5-d]pyrimidin-2-one;
- 7- (N,N-bismethoxyethylamino)-5-methyl-3-(2,4,6-trimethyl)phenylthiazolo[4,5-d]pyrimidin-2-one; and,
- 20 7- (N-cyclopropylmethyl-N-propyl) amino-5-methyl-3-(2,4,6-trimethyl)phenylthiazolo[4,5-d]pyrimidin-2-one;
- 25 or a pharmaceutically acceptable salt form thereof.

30 In another embodiment, the present invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt form thereof.

35 In another embodiment, the present invention provides a method of treating psychiatric disorders and neurological diseases including affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress

disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in a mammal, comprising: administering to the mammal a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides intermediate compounds useful in preparation of the CRF antagonist compounds and processes for making those intermediates, as described in the following description and claims.

The CRF antagonist compounds provided by this invention (and especially labelled compounds of this invention) are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the CRF receptor.

DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all

geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

When any variable (e.g., R⁸) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R⁸, then said group may optionally be substituted with up to two R⁸ groups and R⁸ at each occurrence is selected independently from the definition of R⁸. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example -C_vF_w where v = 1 to 3 and w = 1 to (2v+1)). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and

pentachloroethyl. "Alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxo, and s-pentoxo. "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl and the like. "Alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl, propynyl and the like.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counter-ion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate, and the like.

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3- to 8-membered monocyclic or 7- to 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle" or "heterocyclic system" is intended to mean a stable 5- to 7- membered monocyclic or 7- to 10-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results

in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, a nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic system" is intended to mean a stable 5- to 7- membered monocyclic or 7- to 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, 1H-indazole, 2-pyrrolidinyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidinyl, 4aH-carbazole, 4H-quinolizinyl, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolonyl, carbazolyl, 4aH-carbazolyl, β -carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinylperimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidinyl, 4-piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridoazole, pyridoimidazole, pyridothiazole,

pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl. Preferred heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, indolyl, benzimidazolyl, 1*H*-indazolyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, or isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic,

lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and
5 the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting
10 the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of
15 suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are intended to include any covalently bonded carriers which release the active parent drug according to
20 formula (I) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of formula (I) are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved,
25 either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of formula (I) wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug or compound of formula (I) is
30 administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formula (I), and the like.

35 Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. A stable compound or stable structure is meant to imply a compound that is sufficiently robust to survive

isolation to a useful degree of purity from a reaction mixture, and formulation into an effective therapeutic agent.

The term "therapeutically effective amount" of a compound of this invention means an amount effective to antagonize
5 abnormal level of CRF or treat the symptoms of affective disorder, anxiety or depression in a host.

SYNTHESIS

The compounds of the present invention can be prepared in
10 a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those
15 skilled in the art. Preferred methods include but are not limited to those methods described below. Each of the references cited below are hereby incorporated herein by reference.

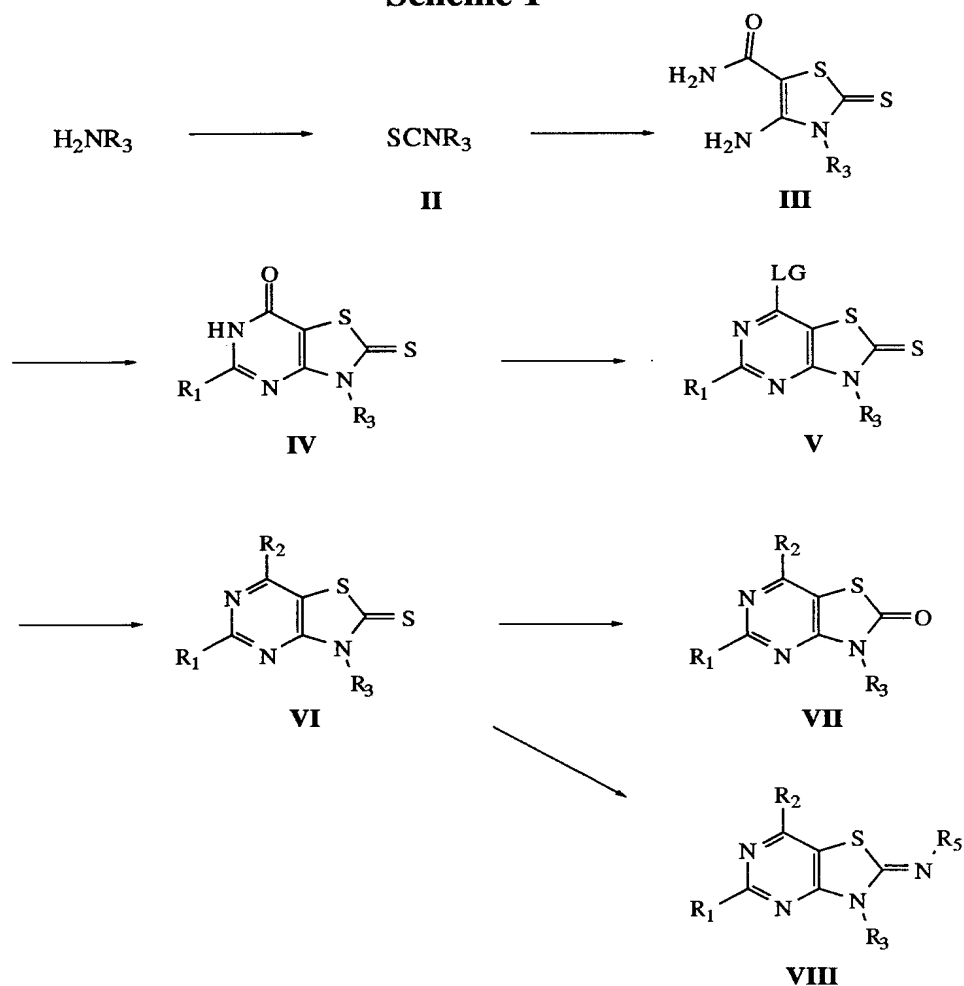
The novel substituted bicyclic thiazolo[4,5]pyrimidines
20 and pyridines of formula (I) of this invention can be prepared by one of the general schemes outlined below (Schemes 1-2).

Compounds of the formula (I), wherein X is N and R³ = phenyl, pyridyl or pyrimidyl can be prepared as shown in Scheme 1. Treatment of anilines, aminopyridines or
25 aminopyrimidines with thiophosgene readily generates the corresponding isothiocyanates (II). Cyclization with elemental sulfur, triethylamine, and cyanoacetamide via the methodology of Gewald (*J. Prakt. Chem.* **1966**, 32, 26-30) affords the thiazolothiones (III). These derivatives can be
30 treated with reagents such as refluxing acetic acid or a trialkylorthoformate or acetate, or any appropriately R¹ substituted carboxylic acid to form the thiazolo[4,5] - pyrimidone thiones (IV). Treatment of the pyrimidone group in (IV) with reagents such as phosphorous oxychloride,
35 phosphorous oxybromide, methanesulfonyl chloride, *p*-toluenesulfonyl chloride, or trifluormethanesulfonic anhydride can provide compounds of formula (V), wherein the LG is a

leaving group and is, respectively, chloro, bromo, methanesulfonate, *p*-toluenesulfonate, or triflate.

The resulting leaving group can then be replaced with a nucleophile such as an amine, an alcohol, or an organolithium, organomagnesium, organosodium, organopotassium, an alkyl cuprate or in general, an organometallic reagent to the corresponding compound (V). Conditions which may facilitate this transformation include the optional presence of bases such as sodium hydride, triethylamine, diisopropylethylamine, or potassium carbonate, or a metallic bis(trimethylsilyl)amide wherein the metal can be sodium, lithium, or potassium.

Scheme 1



These reactions may be conducted neat, or in the optional presence of solvents such as but not limited to tetrahydrofuran, dimethylformamide, dimethylsulfoxide, ethylene glycol, methylene chloride, acetonitrile, or ethanol at room temperature or at elevated temperature up to the boiling point of the solvent employed. One skilled in the art of organic synthesis will readily understand the optimal combinations of these conditions to prepare a number of compounds of Formula (VI) with R₂ variations, and can refer to the review of Brown, D.J. (*Comprehensive Heterocyclic Chemistry*, Katritzky, A.R., et al., Eds., Pergamon Press, Oxford, **1984**, 3, 57-156).

Optionally, where R₂ is an aryl or substituted aryl, the precursor aryl boronic acid (R₂-B(OH)₂) may be coupled to halo-intermediate of formula (V) using catalytic amounts of tetrakis(triphenylphosphine)palladium, as taught by Suzuki, et al. (*Synthetic Communications*, **1981**, 11, 513-519).

Additionally, carbon substituents represented by R₂ may be introduced into compound of formula (V) by treatment with a sodium salt (generated by the use of a base such as sodium ethoxide, sodium hydride or sodium bis(trimethylsilyl)amide) of an active methylene or methine reagent (i.e. where the substituents are groups which stabilize adjacent anions, such as keto, carboalkoxy, cyano, alkyl- or aryl-sulfonyl, etc.).

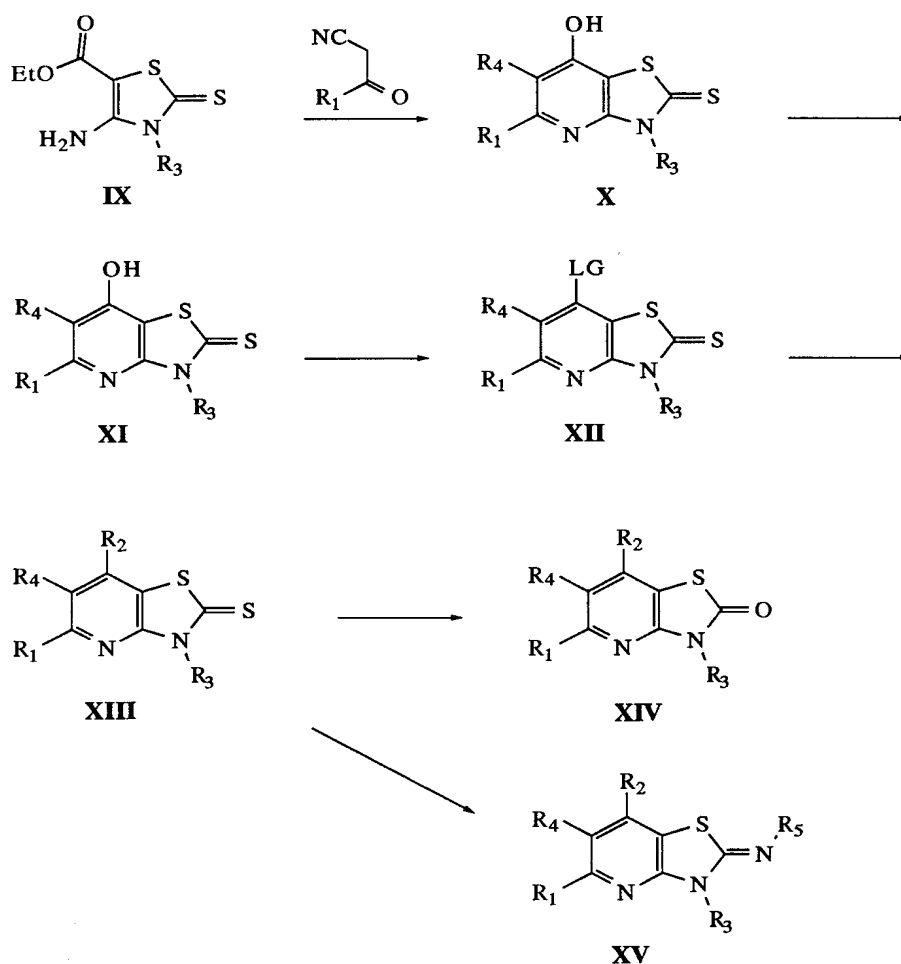
The resulting compounds of formula (VI) may be further modified by conversion of the stabilizing groups into substituents defined in the scope of formula (I). Those skilled in the art of organic synthesis should readily understand the possible variations of these conversions in preparing a number of compounds of formula (VI), and can consult the text of Larock, R.C. (*Comprehensive Organic Transformations*, VCH Publishers, New York, **1989**).

Thiones of compound (VI) can be replaced with oxygen by activation with a strong methylating reagent such as dimethyl sulfate and subsequent water hydrolysis to afford the thiazolones (VII). This chemistry can be carried out at ambient temperature, or more commonly, at or above 100°C. Alternatively, the thione of compound (VI) can again be

activated with a strong methylating reagent such as dimethyl sulfate and treated with amines as described by Gewald (*Monatshefte fur Chemie*, **1981**, 112, 1393-1404) providing thiazoloimines (VIII).

- 5 Compounds of the formula (I), wherein X is C-R⁴ and R³ is phenyl, pyridyl or pyrimidyl can be prepared as shown in Scheme 2. Preparation of thiazolothiones (IX) is accomplished utilizing the same methodology described in Scheme 1 for the preparation of compounds of formula (III), with the
- 10 replacement of a lower alkyl (typically C₁-C₄) cyanoacetate for cyanoacetamide. Preparation of compounds of formula

Scheme 2



- 15 (X, R⁴=CN) readily occurs with the treatment of thiazolothiones (IX) with another equivalent of an active

methylene reagent as depicted in the Scheme. This methodology is amply illustrated in the work of Mohareb, R.M. et al. (*J. Chem. Research*, **1994**, 126-127).

Removal of the cyano group of (X, R⁴) can be accomplished with either acid (for example, but not limited to, hydrochloric, sulphuric, or acetic acid) or base (for example, but not limited to, sodium hydroxide) in the presence of elevated temperature to afford the hydroxypyridine (XI, R⁴=H), and one skilled in the art of organic synthesis will readily understand the optimal conditions for effecting this transformation, or can consult the classic text of Vogel, A.I. (*A Textbook of Practical Organic Chemistry*, Longman Group Limited, London, **1956**, 805).

Compound of formula (XII) can then be prepared by the route described in Scheme 1 for the preparation of compound of formula (V). Furthermore, compound of formula (XIII) can be prepared by the route described in Scheme 1 for the preparation of compound of formula (VI) where R₂ is incorporated into the core structure. Additionally, utilizing the chemistry and references detailed in Scheme 1 for the preparation of compounds of formula (VII) and (VIII), so to can compounds of formula (XIV) and (XV) be prepared.

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

Example 1

3-(2-Bromo-4-isopropyl)phenyl-5-methyl-7-morpholino-thiazolo[4,5-d]pyrimidin-2-thione:

Part A: 2-Bromo-4-isopropylaniline (5.0 g, 23.4 mmol) was added to sodium carbonate (7.4 g, 70.2 mmol) in anhydrous dimethylformamide (125 ml) at 0°C. Addition of thiophosgene (2.7 ml, 35.1 mmol) via syringe discharged the initial red color. The reaction was stirred 20 minutes at 0°C, poured onto 600 ml water, and extracted with ethyl acetate (4 X 100 ml). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated *in-vacuo*. The

crude oil was chromatographed on silica gel (300 g; hexanes) affording the desired product as a pale yellow oil, 5.2 g (87%). FT-IR (neat): 2060 (s) cm^{-1} , ($-\text{N}=\text{C}=\text{S}$).

5 **Part B:** To anhydrous dimethylformamide (20 ml) was added triethylamine (2.45 ml, 17.6 mmol) and cyanoacetamide (1.7 g, 20.7 mmol) followed by stirring at room temperature for 10 minutes. Addition of elemental sulfur (655 mg, 20.4 mmol) induced a strong red/brown color. The reaction was
10 stirred 45 minutes, charged with the isothiocyanate produced in Part A (5.2 g, 20.4 mmol), and stirred an additional 2.5 hours at room temperature. The reaction was poured into water (600 ml), and saturated sodium chloride solution (100 ml) and extracted with ethyl acetate (4 X 100 ml). The combined
15 organic extracts were washed with water (2 X 100 ml), saturated sodium chloride solution (1 X 100 ml), dried over anhydrous magnesium sulfate, filtered, and concentrated *in-vacuo*. Chromatography on silica gel (600 g; 2/1 ethyl acetate/hexanes) gave 5.9 g (78%) of desired product; mp
20 205°C. Anal. Calcd. for $\text{C}_{13}\text{H}_{14}\text{N}_3\text{O}_1\text{S}_2\text{Br}_1$: C, 41.94; H, 3.79; N, 11.29. Found: C, 41.88; H, 3.64; N, 11.01.

Part C: To the thiazolothione produced in Part B (5.9 g, 16.0 mmol) was added distilled acetic anhydride (35 ml).
25 The reaction was refluxed 3 hours, stored overnight in a freezer, then diluted with water (300 ml) and extracted with ethyl acetate (4 X 70 ml). The combined organic extracts were washed with water (5 X 70 ml), and brine (1 X 50 ml), and dried over anhydrous magnesium sulfate, filtered and
30 concentrated *in-vacuo*. The crude solid obtained was used without further purification in Part D.

Part D: The pyrimidone from Part C (15.97 mmol) was treated with phosphorous oxychloride (50 ml) and brought to
35 reflux for 2 hours. The reaction was subsequently poured very cautiously onto 1.4 liters ice/water and allowed to stir overnight. The resultant solid was filtered and dried to constant weight affording 5.7 g (85%). Recrystallization from

hexanes gave crystals, mp 143.5-145°C. Anal. Calcd. for $C_{15}H_{14}N_3S_2Cl_1Br_1$: C, 43.33; H, 3.39; N, 10.11. Found: C, 43.44; H, 3.01; N, 9.93.

5 **Part E:** The product from Example 1, Part D (250 mg, 0.6 mmol) was dissolved in anhydrous acetone (6 ml), treated with morpholine (106 μ l, 1.2 mmol), and the reaction refluxed 2 hours. Concentration under a stream of nitrogen gave a yellow powder. The solid was taken up in water (100 ml) and
10 extracted with methylene chloride (3 X 50 ml). The combined organic extracts were washed with saturated sodium chloride solution (1 X 30 ml), dried over anhydrous magnesium sulfate, filtered and concentrated *in-vacuo* to give a beige solid. Recrystallization from ethyl acetate gave opaque crystals, 125
15 mg (45%), mp 220-221.5°C. Anal. Calcd. for $C_{19}H_{21}N_4S_2Br_1O_1$: C, 49.03; H, 4.55; N, 12.04. Found: C, 49.09; H, 4.42; N, 12.03.

Example 2

20 **3-(2-Bromo-4-isopropyl)phenyl-7-(N-cyclopropylmethyl-N-propyl)amino-5-methylthiazolo[4,5-d]pyrimidin-2-thione:**

The product from Example 1, Part D (2.25 g, 5.41 mmol) and N-cyclopropylmethyl-N-propylamine (1.55 ml, 10.82 mmol)
25 were coupled using the same method described in Example 2 to provide the desired product, 2.38 g (97%), as an off white solid. Recrystallization from diethyl ether gave crystals, mp 117-122°C. Anal. Calcd. for $C_{22}H_{27}N_4S_2Br_1$: C, 53.76; H, 5.54; N, 11.40. Found: C, 53.76; H, 5.46; N, 11.25.

30

Example 3

3-(2-Bromo-4-isopropyl)phenyl-7-(N,N-diethylamino)-5-methyl-thiazolo[4,5-d]pyrimidin-2-thione:

The product from Example 1, Part D (2.74 g, 6.59 mmol)
35 and diethylamine (1.36 ml, 13.2 mmol) were coupled using the same method described in Example 2. Chromatography of the crude solid on silica gel (600 g; 1/9 ethyl acetate/hexanes) gave 2.31 g (78%) of an off white solid. Recrystallization

from diethyl ether gave crystals, mp 138-140°C. Anal. Calcd. for C₁₉H₂₃N₄S₂Br₁: C, 50.55; H, 5.15; N, 12.41. Found: C, 50.39; H, 5.15; N, 12.22.

5

Example 4**7-(N,N-bismethoxyethylamino)-3-(2-bromo-4-isopropyl)phenyl-5-methylthiazolo[4,5-d]pyrimidin-2-thione:**

The product from Example 1, Part D (275 mg, 0.66 mmol) and bis(methoxyethyl)amine (195 µl, 1.32 mmol) were coupled using the same method described in Example 2. Chromatography of the crude material on silica gel (50 g; 1/2 ethyl acetate/hexanes) gave the product; 338 mg (100%). Recrystallization from diethyl ether gave crystals, mp 121-123°C. Anal. Calcd. for C₂₁H₂₇N₄O₂S₂Br₁: C, 49.31; H, 5.32; N, 10.95. Found: C, 49.42; H, 5.20; N, 10.68.

15

Example 5**3-(2-Bromo-4-isopropyl)phenyl-7-(N-butyl-N-ethyl)amino-5-methylthiazolo[4,5-d]pyrimidin-2-thione:**

The product from Example 1, Part D (300 mg, 0.72 mmol) and N-butyl-N-ethylamine (197 µl, 1.44 mmol) were coupled using the same method described in Example 2. Chromatography on silica gel (50 g, 1/9 ethyl acetate/hexanes) gave 331 mg (96%) of the product as an oil. Crystallization was achieved from diethyl ether/hexanes, mp 98-101.5°C. Anal. Calcd. for C₂₁H₂₇N₄S₂Br₁: C, 52.60; H, 5.68; N, 11.68. Found: C, 52.81; H, 5.70; N, 11.62.

25

Example 6**3-(2-Bromo-4-isopropyl)phenyl-7-(N,N-di-sec-butylamine)-5-methylthiazolo[4,5-d]pyrimidin-2-thione:**

The product from Example 1, Part D (300 mg, 0.72 mmol) and di-secbutylamine (252 µl, 1.44 mmol) were coupled using the same method described in Example 2. Chromatography on silica gel (50 g, 1/9 ethyl acetate / hexanes) gave the product as a crystalline solid, 343 mg (94%), mp 181-182.5°C. Anal. Calcd. for C₂₃H₃₁N₄S₂Br₁: C, 54.43; H, 6.16; N, 11.04. Found: C, 54.43; H, 6.00; N, 10.85.

35

Example 7**7-(N,N-diethylamino)-5-methyl-3-(2,4,6-trimethyl)phenyl thiazolo[4,5-d]pyrimidin-2-thione:**

5 **Part A:** 2,4,6-Trimethylaniline (5.0 g, 37 mmol) was treated with sodium carbonate (11.8 g, 111.1 mmol) and thiophosgene (4.23 ml, 55.5 mmol) as described in Example 1, Part A. The crude oil was chromatographed on silica gel (350 g; hexanes) affording the desired product, 6.0 g (92%). FT-IR
10 (neat): 2152 (s) cm^{-1} , (-N=C=S).

Part B: The isothiocyanate formed in Part A (5.5 g, 31.2 mmol) was treated with cyanoacetamide (2.6 g, 31.2 mmol), triethylamine (3.76 ml, 27 mmol) and elemental sulfur (1.0 g,
15 31.2 mmol) in dimethyl-formamide (32 ml) as described in Example 1, Part B. The crude yellow/green solid was chromatographed in two portions. A 4 g portion was chromatographed on silica gel (300 g; 2/1 ethyl acetate/hexanes) and a c. 3 g portion was chromatographed on
20 silica gel (300 g; 2/1 ethyl acetate/ hexanes), to afford a combined 6.1 g (67%) desired product, mp 205-206°C. Anal. Calcd. for $\text{C}_{13}\text{H}_{15}\text{N}_3\text{S}_2\text{O}_1$: C, 53.22; H, 5.15. Found: C, 53.08; H, 5.17.

25 **Part C:** The thiazolothione produced in Part B (6.1 g, 21.7 mmol) was treated with acetic anhydride (61 ml) and refluxed for 3 hours. The reaction was cooled in an ice bath, the resulting precipitate filtered and dried to constant weight affording 3.3 g (48%) as a yellow solid.

30 **Part D:** The pyrimidone from Part C (3.5 g, 11.1 mmol) was treated with phosphorous oxychloride (35 ml) and refluxed for 2.5 hours. The reaction was cooled and transferred cautiously onto 1 liter of ice/water, and stirred overnight.
35 The resultant precipitate was filtered and dried to constant weight giving 3.3 g (89%), mp 162.5-163.5°C. Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{N}_3\text{S}_2\text{Cl}_1$: C, 53.64; H, 4.20; N, 12.51. Found: C, 53.19; H, 4.17; N, 12.33.

Part E: The product from Example 8, Part D (1.13 g, 3.35 mmol) and diethylamine (693 μ l, 6.7 mmol) were coupled using the same method described in Example 2. Chromatography on silica gel (200 g; 1/9 ethyl acetate/hexanes) gave the product, 1.20 g (96%) as an amorphous solid. Crystals were afforded from dissolution and standing in hexanes, mp 129.5-131.5°C. Anal. Calcd. for $C_{19}H_{24}N_4S_2$: C, 61.25; H, 6.49; N, 15.04. Found: C, 61.26; H, 6.47; N, 15.11.

Example 8

7-(N,N-bismethoxyethylamino)-5-methyl-3-(2,4,6-trimethyl) phenylthiazolo[4,5-d]pyrimidin-2-thione:

The product from Example 8, Part D (1.05 g, 3.13 mmol) and bis(methoxyethyl)amine (925 μ l, 6.26 mmol) were coupled using the same method described in Example 2. Chromatography on silica gel (200 g; 2/8 ethyl acetate/hexanes) gave the product as a viscous oil, 1.33 g (99%). Anal. Calcd. for $C_{21}H_{28}N_4O_2S_2$: C, 58.31; H, 6.52; N, 12.95. Found: C, 58.47; H, 6.44; N, 12.86.

Example 9

7-(N-cyclopropylmethyl-N-propyl)-5-methyl-3-(2,4,6-trimethyl)phenylthiazole[4,5-d]pyrimidin-2-thione:

The product from Example 8, Part D (1.1 g, 3.28 mmol) and N-cyclopropylmethyl-N-propylamine (944 ml, 6.6 mmol) were coupled using the same method described in Example 2. Chromatography on silica gel (200 g; 2/8 ethyl acetate/hexanes) gave the product as an amorphous solid. Anal. Calcd. for $C_{22}H_{28}N_4S_2$: C, 64.04; H, 6.84; N, 13.58. Found: C, 64.31; H, 6.91; N, 13.45.

Example 10

3-(2-Bromo-4-isopropyl)phenyl-7-(N-cyclopropylmethyl-N-propyl)amino-5-methylthiazolo[4,5-d]pyrimidin-2-one:

The product from Example 3 (300 mg, 0.61 mmol) was treated with dimethyl sulfate (113 μ l, 1.22 mmol) and heated in an oil bath at 130°C for 1 hour. To the reaction was added

water (3 ml) followed by refluxing 2 hours. The cooled reaction was diluted with water (10 ml) and extracted with ethyl acetate (3 X 10 ml). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in-vacuo*. The resultant oil was chromatographed on silica gel (150 g; 2/8 ethyl acetate/ hexanes) to give 183 mg (62%) of the desired product as an amorphous solid. The product was crystallized and recrystallized from hexanes providing colorless opaque crystals, mp 113-115°C. Anal. Calcd. for C₂₂H₂₇N₄S₁O₁Br₁: C, 55.58; H, 5.72; N, 11.78. Found: C, 55.53; H, 5.83; N, 11.47.

Example 11

7-(N,N-bismethoxyethylamino)-3-(2-bromo-4-isopropyl)phenyl-5-methylthiazolo[4,5-d]pyrimidin-2-one:

The product from Example 5 (250 mg, 0.49 mmol) was treated with dimethyl sulfate (93 µl, 1.0 mmol) under the same conditions described in Example 12. The crude oil was chromatographed on silica gel (25 mg; 1/2 ethyl acetate/hexanes) to afford the desired product, 16 mg (6%) as a viscous oil. CI-HRMS calcd. for C₂₁H₂₈N₄O₃S₁Br₁ (M+H): 495.1065. Found: 495.1077.

Example 12

3-(2-Bromo-4-isopropyl)phenyl-7-(N,N-diethylamino)-5-methylthiazolo[4,5-d]pyrimidin-2-one:

The product from Example 4 (490 mg, 1.1 mmol) was treated with dimethyl sulfate (202 µl, 2.18 mmol) under the same conditions described in Example 12. The crude oil was chromatographed on silica gel (30 g; 1/9 ethyl acetate/hexanes) to afford 235 mg (50%) of the desired product as an amorphous solid. Anal. Calcd. for C₁₉H₂₃N₄S₁O₁Br₁: C, 52.41; H, 5.32; N, 12.87. Found: C, 52.69; H, 5.46; N, 12.62.

Example 13

7-(N,N-diethylamino)-5-methyl-3-(2,4,6-trimethyl)phenyl thiazolo[4,5-d]pyrimidin-2-one:

The product from Example 9 (600 mg, 1.61 mmol) was treated with dimethyl sulfate (300 μ l, 3.22 mmol) under the same conditions described in Example 12. The crude oil was chromatographed on silica gel (30 g; 1/9 ethyl acetate/hexanes) to give the product, 255 mg (44%) as an amorphous solid. Anal. Calcd. for $C_{19}H_{24}N_4O_1S_1$: C, 64.02; H, 6.79; N, 15.72. Found: C, 64.24; H, 6.67; N, 15.63.

Example 14

7-(N,N-bismethoxyethylamino)-5-methyl-3-(2,4,6-trimethyl) phenylthiazolo[4,5-d]pyrimidin-2-one:

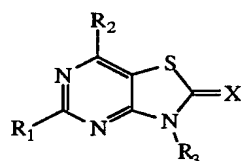
The product from Example 10 (663 mg, 1.53 mmol) was treated with dimethyl sulfate (284 μ l, 3.06 mmol) under the same conditions described in Example 12. The crude oil was chromatographed on silica gel (35 g; 1/2 ethyl acetate/hexanes) to give the product, 67 mg (11%), as a viscous oil. CI-HRMS calcd. for $C_{21}H_{28}N_4O_2S_2$ (M+H): 417.1960. Found: 417.1947.

Example 15

7-(N-cyclopropylmethyl-N-propyl)amino-5-methyl-3-(2,4,6-trimethyl)phenylthiazolo[4,5-d]pyrimidin-2-one:

The product from Example 11 (600 mg; 1.45 mmol) was treated with dimethyl sulfate (270 μ l; 2.91 mmol) under the same conditions described in Example 12. The crude oil was chromatographed on silica gel (70 g; 2/8 ethyl acetate/hexanes) to give the product, 124 mg (22%) as a crystalline solid, mp 93-94°C. Anal. Calcd. for $C_{22}H_{28}N_4O_1S_1$: C, 66.64; H, 7.12; N, 14.13. Found: C, 66.79; H, 7.08; N, 13.93.

Table 1

5 Key for R³ in the following Table:

A: 2-bromo-4-isopropylphenyl

C: 2,4,6-trimethylphenyl

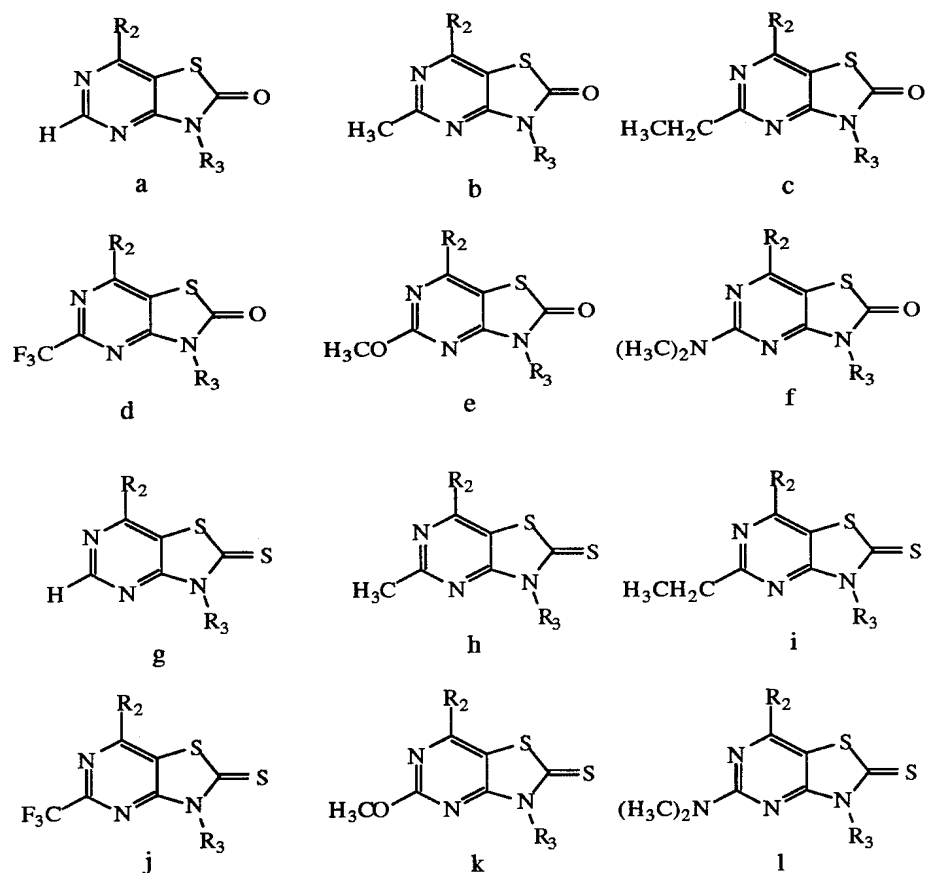
| | Ex. | X | R ₁ | R ₂ | R ₃ | Mp, °C |
|----|-----|---|----------------|---|----------------|--------------|
| 10 | 1 | S | Me | morpholino | A | 220-221.5 |
| | 2 | S | Me | N(Pr)CH ₂ cycloPr | A | 117-122 |
| | 3 | S | Me | NEt ₂ | A | 138-140 |
| | 4 | S | Me | N(CH ₂ CH ₂ OMe) ₂ | A | 125-126.5 |
| | 5 | S | Me | NBuEt | A | 98-101.5 |
| 15 | 6 | S | Me | N(di-secbutyl) ₂ | A | 181-182.5 |
| | 7 | S | Me | NEt ₂ | C | 129.5-131 |
| | 8 | S | Me | N(CH ₂ CH ₂ OMe) ₂ | C | Oil; C,H,N |
| | 9 | S | Me | N(Pr)CH ₂ cycloPr | C | Amor.; C,H,N |
| | 10 | O | Me | N(Pr)CH ₂ cycloPr | A | 113-115 |
| 20 | 11 | O | Me | N(CH ₂ CH ₂ OMe) ₂ | A | Oil; HRMS |
| | 12 | O | Me | NEt ₂ | A | Amor.; C,H,N |
| | 13 | O | Me | NEt ₂ | C | Oil; C,H,N |
| | 14 | O | Me | N(CH ₂ CH ₂ OMe) ₂ | C | Oil; HRMS |
| | 15 | O | Me | N(Pr)CH ₂ cycloPr | C | 93-94 |

25

The following table contains representative examples of the present invention. Each entry in the table is intended to be paired with each formulae at the start of the table. For example, example 1 in Table 2 is intended to be paired with each of formulae a-x.

30

Table 2



5

Key for R³ in the following Tables:

- | | | |
|----|----|---|
| | A: | 2-bromo-4-isopropylphenyl |
| 10 | B: | 2-chloro-4,6-dimethoxyphenyl |
| | C: | 2,4,6-trimethylphenyl |
| | D: | 2-bromo-4,6-dimethoxyphenyl |
| | E: | 2,4,6-trichlorophenyl |
| | F: | 4-bromo-2,6-dichlorophenyl |
| 15 | G: | 2,4,6-trimethoxyphenyl |
| | H: | 2,6-dichloro-4-trifluoromethylphenyl |
| | I: | 2,4-dibromo-6-methoxyphenyl |
| | J: | 2-bromo-4-isopropyl-6-methoxyphenyl |
| | K: | 2,4-dimethoxy-3-pyridyl |
| 20 | L: | 4-dimethylamino-2-trifluoromethylphenyl |

| | Ex. | R ₂ | R ₃ |
|----|-----|--|----------------|
| | 1 | CH(CH ₂ CH ₃) ₂ A | |
| | 2 | OCH(CH ₂ CH ₃) ₂ | A |
| | 3 | N(CH ₂ CH ₃) ₂ | A |
| 5 | 4 | N(H)CH ₂ CH ₂ CH ₃ | A |
| | 5 | N(CH ₂ CH ₂ OCH ₃)(CH ₂ CH ₂ CH ₃) | A |
| | 6 | N(CH ₂ CH ₃)CH ₂ CH ₂ CH ₂ CH ₃ | A |
| | 7 | NHCH(CH ₂ CH ₃)CH ₂ SO ₂ Me | A |
| | 8 | N(CH ₂ CH ₂ OMe) ₂ | A |
| 10 | 9 | N(Pr)CH ₂ cycloPr | A |
| | 10 | N(CH ₂ CH ₃)CH ₂ SO ₂ Me | A |
| | 11 | CH(CO ₂ CH ₂ CH ₃) ₂ | A |
| | 12 | CH(CH ₂ OCH ₃) ₂ | A |
| | 13 | 4-methoxyphenyl | A |
| 15 | 14 | morpholino | A |
| | 15 | thiomorpholino | A |
| | 16 | phenyl | A |
| | 17 | 2-NO ₂ phenyl A | |
| | 18 | 2-CF ₃ phenyl A | |
| 20 | 19 | 4-pyridyl | A |
| | 20 | cyclopentyl A | |
| | 21 | cyclohexyl | A |
| | 22 | NH(cyclopentyl) | A |
| | 23 | N(Et)CH ₂ cycloPr | A |
| 25 | 24 | NHCH(CH ₃)CH ₂ CH ₃ | A |
| | 25 | NCH(CH ₂ CH ₃) ₂ | A |
| | 26 | N(CH ₂ CH ₂ CH ₃) ₂ | A |
| | 27 | N(CH ₂ CH ₂ OMe)CH ₂ CH ₂ CH ₂ OMe | A |
| | 28 | CH(CH ₂ CH ₃) ₂ B | |
| 30 | 29 | OCH(CH ₂ CH ₃) ₂ | B |
| | 30 | N(CH ₂ CH ₃) ₂ | B |
| | 31 | N(H)CH ₂ CH ₂ CH ₃ | B |
| | 32 | N(CH ₂ CH ₂ OCH ₃)(CH ₂ CH ₂ CH ₃) | B |
| | 33 | N(CH ₂ CH ₃)CH ₂ CH ₂ CH ₂ CH ₃ | B |
| 35 | 34 | NHCH(CH ₂ CH ₃)CH ₂ SO ₂ Me | B |
| | 35 | N(CH ₂ CH ₂ OMe) ₂ | B |
| | 36 | N(Pr)CH ₂ cycloPr | B |
| | 37 | N(CH ₂ CH ₃)CH ₂ SO ₂ Me | B |

| | | | |
|----|----|--|---|
| | 38 | $\text{CH}(\text{CO}_2\text{CH}_2\text{CH}_3)_2$ | B |
| | 39 | $\text{CH}(\text{CH}_2\text{OCH}_3)_2$ | B |
| | 40 | 4-methoxyphenyl | B |
| | 41 | morpholino | B |
| 5 | 42 | thiomorpholino | B |
| | 43 | phenyl | B |
| | 44 | 2-NO ₂ phenyl B | |
| | 45 | 2-CF ₃ phenyl B | |
| | 46 | 4-pyridyl | B |
| 10 | 47 | cyclopentyl B | |
| | 48 | cyclohexyl | B |
| | 49 | NH(cyclopentyl) | B |
| | 50 | N(Et)CH ₂ cycloPr | B |
| | 51 | NHCH(CH ₃)CH ₂ CH ₃ | B |
| 15 | 52 | NCH(CH ₂ CH ₃) ₂ | B |
| | 53 | N(CH ₂ CH ₂ CH ₃) ₂ | B |
| | 54 | N(CH ₂ CH ₂ OMe)CH ₂ CH ₂ CH ₂ OMe | B |
| | 55 | $\text{CH}(\text{CH}_2\text{CH}_3)_2$ C | |
| | 56 | $\text{OCH}(\text{CH}_2\text{CH}_3)_2$ | C |
| 20 | 57 | $\text{N}(\text{CH}_2\text{CH}_3)_2$ | C |
| | 58 | N(H)CH ₂ CH ₂ CH ₃ | C |
| | 59 | N(CH ₂ CH ₂ OCH ₃)(CH ₂ CH ₂ CH ₃) | C |
| | 60 | N(CH ₂ CH ₃)CH ₂ CH ₂ CH ₂ CH ₃ | C |
| | 61 | NHCH(CH ₂ CH ₃)CH ₂ SO ₂ Me | C |
| 25 | 62 | N(CH ₂ CH ₂ OMe) ₂ | C |
| | 63 | N(Pr)CH ₂ cycloPr | C |
| | 64 | N(CH ₂ CH ₃)CH ₂ SO ₂ Me | C |
| | 65 | $\text{CH}(\text{CO}_2\text{CH}_2\text{CH}_3)_2$ | C |
| | 66 | $\text{CH}(\text{CH}_2\text{OCH}_3)_2$ | C |
| 30 | 67 | 4-methoxyphenyl | C |
| | 68 | morpholino | C |
| | 69 | thiomorpholino | C |
| | 70 | phenyl | C |
| | 71 | 2-NO ₂ phenyl C | |
| 35 | 72 | 2-CF ₃ phenyl C | |
| | 73 | 4-pyridyl | C |
| | 74 | cyclopentyl C | |
| | 75 | cyclohexyl | C |

| | | | |
|----|-----|--|---|
| | 76 | NH(cyclopentyl) | C |
| | 77 | N(Et)CH ₂ cycloPr | C |
| | 78 | NHCH(CH ₃)CH ₂ CH ₃ | C |
| | 79 | NCH(CH ₂ CH ₃) ₂ | C |
| 5 | 80 | N(CH ₂ CH ₂ CH ₃) ₂ | C |
| | 81 | N(CH ₂ CH ₂ OMe)CH ₂ CH ₂ CH ₂ OMe | C |
| | 82 | CH(CH ₂ CH ₃) ₂ D | |
| | 83 | OCH(CH ₂ CH ₃) ₂ | D |
| | 84 | N(CH ₂ CH ₃) ₂ | D |
| 10 | 85 | N(H)CH ₂ CH ₂ CH ₃ | D |
| | 86 | N(CH ₂ CH ₂ OCH ₃)(CH ₂ CH ₂ CH ₃) | D |
| | 87 | N(CH ₂ CH ₃)CH ₂ CH ₂ CH ₂ CH ₃ | D |
| | 88 | NHCH(CH ₂ CH ₃)CH ₂ SO ₂ Me | D |
| | 89 | N(CH ₂ CH ₂ OMe) ₂ | D |
| 15 | 90 | N(Pr)CH ₂ cycloPr | D |
| | 91 | N(CH ₂ CH ₃)CH ₂ SO ₂ Me | D |
| | 92 | CH(CO ₂ CH ₂ CH ₃) ₂ | D |
| | 93 | CH(CH ₂ OCH ₃) ₂ | D |
| | 94 | 4-methoxyphenyl | D |
| 20 | 95 | morpholino | D |
| | 96 | thiomorpholino | D |
| | 97 | phenyl | D |
| | 98 | 2-NO ₂ phenyl D | |
| | 99 | 2-CF ₃ phenyl D | |
| 25 | 100 | 4-pyridyl | D |
| | 101 | cyclopentyl D | |
| | 102 | cyclohexyl | D |
| | 103 | NH(cyclopentyl) | D |
| | 104 | N(Et)CH ₂ cycloPr | D |
| 30 | 105 | NHCH(CH ₃)CH ₂ CH ₃ | D |
| | 106 | NCH(CH ₂ CH ₃) ₂ | D |
| | 107 | N(CH ₂ CH ₂ CH ₃) ₂ | D |
| | 108 | N(CH ₂ CH ₂ OMe)CH ₂ CH ₂ CH ₂ OMe | D |
| | 109 | CH(CH ₂ CH ₃) ₂ E | |
| 35 | 110 | OCH(CH ₂ CH ₃) ₂ | E |
| | 111 | N(CH ₂ CH ₃) ₂ | E |
| | 112 | N(H)CH ₂ CH ₂ CH ₃ | E |
| | 113 | N(CH ₂ CH ₂ OCH ₃)(CH ₂ CH ₂ CH ₃) | E |

| | | | |
|----|-----|----------------------------------|---|
| | 114 | $N(CH_2CH_3)CH_2CH_2CH_2CH_3$ | E |
| | 115 | $NHCH(CH_2CH_3)CH_2SO_2Me$ | E |
| | 116 | $N(CH_2CH_2OMe)_2$ | E |
| | 117 | $N(Pr)CH_2cycloPr$ | E |
| 5 | 118 | $N(CH_2CH_3)CH_2SO_2Me$ | E |
| | 119 | $CH(CO_2CH_2CH_3)_2$ | E |
| | 120 | $CH(CH_2OCH_3)_2$ | E |
| | 121 | 4-methoxyphenyl | E |
| | 122 | morpholino | E |
| 10 | 123 | thiomorpholino | E |
| | 124 | phenyl | E |
| | 125 | 2-NO ₂ phenyl E | |
| | 126 | 2-CF ₃ phenyl E | |
| | 127 | 4-pyridyl | E |
| 15 | 128 | cyclopentyl E | |
| | 129 | cyclohexyl | E |
| | 130 | $NH(cyclopentyl)$ | E |
| | 131 | $N(Et)CH_2cycloPr$ | E |
| | 132 | $NHCH(CH_3)CH_2CH_3$ | E |
| 20 | 133 | $NCH(CH_2CH_3)_2$ | E |
| | 134 | $N(CH_2CH_2CH_3)_2$ | E |
| | 135 | $N(CH_2CH_2OMe)CH_2CH_2CH_2OMe$ | E |
| | 136 | $CH(CH_2CH_3)_2 F$ | |
| | 137 | $OCH(CH_2CH_3)_2$ | F |
| 25 | 138 | $N(CH_2CH_3)_2$ | F |
| | 139 | $N(H)CH_2CH_2CH_3$ | F |
| | 140 | $N(CH_2CH_2OCH_3)(CH_2CH_2CH_3)$ | F |
| | 141 | $N(CH_2CH_3)CH_2CH_2CH_2CH_3$ | F |
| | 142 | $NHCH(CH_2CH_3)CH_2SO_2Me$ | F |
| 30 | 143 | $N(CH_2CH_2OMe)_2$ | F |
| | 144 | $N(Pr)CH_2cycloPr$ | F |
| | 145 | $N(CH_2CH_3)CH_2SO_2Me$ | F |
| | 146 | $CH(CO_2CH_2CH_3)_2$ | F |
| | 147 | $CH(CH_2OCH_3)_2$ | F |
| 35 | 148 | 4-methoxyphenyl | F |
| | 149 | morpholino | F |
| | 150 | thiomorpholino | F |
| | 151 | phenyl | F |

| | | | |
|----|-----|--|---|
| | 152 | 2-NO ₂ phenyl F | |
| | 153 | 2-CF ₃ phenyl F | |
| | 154 | 4-pyridyl | F |
| | 155 | cyclopentyl F | |
| 5 | 156 | cyclohexyl | F |
| | 157 | NH(cyclopentyl) | F |
| | 158 | N(Et)CH ₂ cycloPr | F |
| | 159 | NHCH(CH ₃)CH ₂ CH ₃ | F |
| | 160 | NCH(CH ₂ CH ₃) ₂ | F |
| 10 | 161 | N(CH ₂ CH ₂ CH ₃) ₂ | F |
| | 162 | N(CH ₂ CH ₂ OMe)CH ₂ CH ₂ CH ₂ OMe | F |
| | 163 | CH(CH ₂ CH ₃) ₂ G | |
| | 164 | OCH(CH ₂ CH ₃) ₂ | G |
| | 165 | N(CH ₂ CH ₃) ₂ | G |
| 15 | 166 | N(H)CH ₂ CH ₂ CH ₃ | G |
| | 167 | N(CH ₂ CH ₂ OCH ₃)(CH ₂ CH ₂ CH ₃) | G |
| | 168 | N(CH ₂ CH ₃)CH ₂ CH ₂ CH ₂ CH ₃ | G |
| | 169 | NHCH(CH ₂ CH ₃)CH ₂ SO ₂ Me | G |
| | 170 | N(CH ₂ CH ₂ OMe) ₂ | G |
| 20 | 171 | N(Pr)CH ₂ cycloPr | G |
| | 172 | N(CH ₂ CH ₃)CH ₂ SO ₂ Me | G |
| | 173 | CH(CO ₂ CH ₂ CH ₃) ₂ | G |
| | 174 | CH(CH ₂ OCH ₃) ₂ | G |
| | 175 | 4-methoxyphenyl | G |
| 25 | 176 | morpholino | G |
| | 177 | thiomorpholino | G |
| | 178 | phenyl | G |
| | 179 | 2-NO ₂ phenyl G | |
| | 180 | 2-CF ₃ phenyl G | |
| 30 | 181 | 4-pyridyl | G |
| | 182 | cyclopentyl G | |
| | 183 | cyclohexyl | G |
| | 184 | NH(cyclopentyl) | G |
| | 185 | N(Et)CH ₂ cycloPr | G |
| 35 | 186 | NHCH(CH ₃)CH ₂ CH ₃ | G |
| | 187 | NCH(CH ₂ CH ₃) ₂ | G |
| | 188 | N(CH ₂ CH ₂ CH ₃) ₂ | G |
| | 189 | N(CH ₂ CH ₂ OMe)CH ₂ CH ₂ CH ₂ OMe | G |

| | | | |
|----|-----|--|---|
| | 190 | CH(CH ₂ CH ₃) ₂ H | |
| | 191 | OCH(CH ₂ CH ₃) ₂ | H |
| | 192 | N(CH ₂ CH ₃) ₂ | H |
| | 193 | N(H)CH ₂ CH ₂ CH ₃ | H |
| 5 | 194 | N(CH ₂ CH ₂ OCH ₃)(CH ₂ CH ₂ CH ₃) | H |
| | 195 | N(CH ₂ CH ₃)CH ₂ CH ₂ CH ₂ CH ₃ | H |
| | 196 | NHCH(CH ₂ CH ₃)CH ₂ SO ₂ Me | H |
| | 197 | N(CH ₂ CH ₂ OMe) ₂ | H |
| | 198 | N(Pr)CH ₂ cycloPr | H |
| 10 | 199 | N(CH ₂ CH ₃)CH ₂ SO ₂ Me | H |
| | 200 | CH(CO ₂ CH ₂ CH ₃) ₂ | H |
| | 201 | CH(CH ₂ OCH ₃) ₂ | H |
| | 202 | 4-methoxyphenyl | H |
| | 203 | morpholino | H |
| 15 | 204 | thiomorpholino | H |
| | 205 | phenyl | H |
| | 206 | 2-NO ₂ phenyl H | |
| | 207 | 2-CF ₃ phenyl H | |
| | 208 | 4-pyridyl | H |
| 20 | 209 | cyclopentyl H | |
| | 210 | cyclohexyl | H |
| | 211 | NH(cyclopentyl) | H |
| | 212 | N(Et)CH ₂ cycloPr | H |
| | 213 | NHCH(CH ₃)CH ₂ CH ₃ | H |
| 25 | 214 | NCH(CH ₂ CH ₃) ₂ | H |
| | 215 | N(CH ₂ CH ₂ CH ₃) ₂ | H |
| | 216 | N(CH ₂ CH ₂ OMe)CH ₂ CH ₂ CH ₂ OMe | H |
| | 217 | CH(CH ₂ CH ₃) ₂ I | |
| | 218 | OCH(CH ₂ CH ₃) ₂ | I |
| 30 | 219 | N(CH ₂ CH ₃) ₂ | I |
| | 220 | N(H)CH ₂ CH ₂ CH ₃ | I |
| | 221 | N(CH ₂ CH ₂ OCH ₃)(CH ₂ CH ₂ CH ₃) | I |
| | 222 | N(CH ₂ CH ₃)CH ₂ CH ₂ CH ₂ CH ₃ | I |
| | 223 | NHCH(CH ₂ CH ₃)CH ₂ SO ₂ Me | I |
| 35 | 224 | N(CH ₂ CH ₂ OMe) ₂ | I |
| | 225 | N(Pr)CH ₂ cycloPr | I |
| | 226 | N(CH ₂ CH ₃)CH ₂ SO ₂ Me | I |
| | 227 | CH(CO ₂ CH ₂ CH ₃) ₂ | I |

| | | | |
|----|-----|--|---|
| | 228 | $\text{CH}(\text{CH}_2\text{OCH}_3)_2$ | I |
| | 229 | 4-methoxyphenyl | I |
| | 230 | morpholino | I |
| | 231 | thiomorpholino | I |
| 5 | 232 | phenyl | I |
| | 233 | 2-NO ₂ phenyl I | |
| | 234 | 2-CF ₃ phenyl I | |
| | 235 | 4-pyridyl | I |
| | 236 | cyclopentyl I | |
| 10 | 237 | cyclohexyl | I |
| | 238 | NH(cyclopentyl) | I |
| | 239 | N(Et)CH ₂ cycloPr | I |
| | 240 | NHCH(CH ₃)CH ₂ CH ₃ | I |
| | 241 | NCH(CH ₂ CH ₃) ₂ | I |
| 15 | 242 | N(CH ₂ CH ₂ CH ₃) ₂ | I |
| | 243 | N(CH ₂ CH ₂ OMe)CH ₂ CH ₂ CH ₂ OMe | I |
| | 244 | $\text{CH}(\text{CH}_2\text{CH}_3)_2$ J | |
| | 245 | OCH(CH ₂ CH ₃) ₂ | J |
| | 246 | N(CH ₂ CH ₃) ₂ | J |
| 20 | 247 | N(H)CH ₂ CH ₂ CH ₃ | J |
| | 248 | N(CH ₂ CH ₂ OCH ₃)(CH ₂ CH ₂ CH ₃) | J |
| | 249 | N(CH ₂ CH ₃)CH ₂ CH ₂ CH ₂ CH ₃ | J |
| | 250 | NHCH(CH ₂ CH ₃)CH ₂ SO ₂ Me | J |
| | 251 | N(CH ₂ CH ₂ OMe) ₂ | J |
| 25 | 252 | N(Pr)CH ₂ cycloPr | J |
| | 253 | N(CH ₂ CH ₃)CH ₂ SO ₂ Me | J |
| | 254 | $\text{CH}(\text{CO}_2\text{CH}_2\text{CH}_3)_2$ | J |
| | 255 | $\text{CH}(\text{CH}_2\text{OCH}_3)_2$ | J |
| | 256 | 4-methoxyphenyl | J |
| 30 | 257 | morpholino | J |
| | 258 | thiomorpholino | J |
| | 259 | phenyl | J |
| | 260 | 2-NO ₂ phenyl J | |
| | 261 | 2-CF ₃ phenyl J | |
| 35 | 262 | 4-pyridyl | J |
| | 263 | cyclopentyl J | |
| | 264 | cyclohexyl | J |
| | 265 | NH(cyclopentyl) | J |

| | | | |
|----|-----|--|---|
| | 266 | N(Et)CH ₂ cycloPr | J |
| | 267 | NHCH(CH ₃)CH ₂ CH ₃ | J |
| | 268 | NCH(CH ₂ CH ₃) ₂ | J |
| | 269 | N(CH ₂ CH ₂ CH ₃) ₂ | J |
| 5 | 270 | N(CH ₂ CH ₂ OMe)CH ₂ CH ₂ CH ₂ OMe | J |
| | 271 | CH(CH ₂ CH ₃) ₂ K | |
| | 272 | OCH(CH ₂ CH ₃) ₂ | K |
| | 273 | N(CH ₂ CH ₃) ₂ | K |
| | 274 | N(H)CH ₂ CH ₂ CH ₃ | K |
| 10 | 275 | N(CH ₂ CH ₂ OCH ₃)(CH ₂ CH ₂ CH ₃) | K |
| | 276 | N(CH ₂ CH ₃)CH ₂ CH ₂ CH ₂ CH ₃ | K |
| | 277 | NHCH(CH ₂ CH ₃)CH ₂ SO ₂ Me | K |
| | 278 | N(CH ₂ CH ₂ OMe) ₂ | K |
| | 279 | N(Pr)CH ₂ cycloPr | K |
| 15 | 280 | N(CH ₂ CH ₃)CH ₂ SO ₂ Me | K |
| | 281 | CH(CO ₂ CH ₂ CH ₃) ₂ | K |
| | 282 | CH(CH ₂ OCH ₃) ₂ | K |
| | 283 | 4-methoxyphenyl | K |
| | 284 | morpholino | K |
| 20 | 285 | thiomorpholino | K |
| | 286 | phenyl | K |
| | 287 | 2-NO ₂ phenyl K | |
| | 288 | 2-CF ₃ phenyl K | |
| | 289 | 4-pyridyl | K |
| 25 | 290 | cyclopentyl K | |
| | 291 | cyclohexyl | K |
| | 292 | NH(cyclopentyl) | K |
| | 293 | N(Et)CH ₂ cycloPr | K |
| | 294 | NHCH(CH ₃)CH ₂ CH ₃ | K |
| 30 | 295 | NCH(CH ₂ CH ₃) ₂ | K |
| | 296 | N(CH ₂ CH ₂ CH ₃) ₂ | K |
| | 297 | N(CH ₂ CH ₂ OMe)CH ₂ CH ₂ CH ₂ OMe | K |
| | 271 | CH(CH ₂ CH ₃) ₂ L | |
| | 272 | OCH(CH ₂ CH ₃) ₂ | L |
| 35 | 273 | N(CH ₂ CH ₃) ₂ | L |
| | 274 | N(H)CH ₂ CH ₂ CH ₃ | L |
| | 275 | N(CH ₂ CH ₂ OCH ₃)(CH ₂ CH ₂ CH ₃) | L |
| | 276 | N(CH ₂ CH ₃)CH ₂ CH ₂ CH ₂ CH ₃ | L |

| | | | |
|----|-----|---|---|
| | 277 | NHCH(CH ₂ CH ₃)CH ₂ SO ₂ Me | L |
| | 278 | N(CH ₂ CH ₂ OMe) ₂ | L |
| | 279 | N(Pr)CH ₂ cycloPr | L |
| | 280 | N(CH ₂ CH ₃)CH ₂ SO ₂ Me | L |
| 5 | 281 | CH(CO ₂ CH ₂ CH ₃) ₂ | L |
| | 282 | CH(CH ₂ OCH ₃) ₂ | L |
| | 283 | 4-methoxyphenyl | L |
| | 284 | morpholino | L |
| | 285 | thiomorpholino | L |
| 10 | 286 | phenyl | L |
| | 287 | 2-NO ₂ phenyl L | |
| | 288 | 2-CF ₃ phenyl L | |
| | 289 | 4-pyridyl | L |
| | 290 | cyclopentyl L | |
| 15 | 291 | cyclohexyl | L |
| | 292 | NH(cyclopentyl) | L |
| | 293 | N(Et)CH ₂ cycloPr | L |
| | 294 | NHCH(CH ₃)CH ₂ CH ₃ | L |
| | 295 | NCH(CH ₂ CH ₃) ₂ | L |
| 20 | 296 | N(CH ₂ CH ₂ CH ₃) ₂ | L |
| | 297 | N(CH ₂ CH ₂ OMe)CH ₂ CH ₂ CH ₂ OMe | L |

Utility

Compounds of this invention are expected to have utility in the treatment of imbalances associated with abnormal levels of CRF in patients suffering from depression, affective disorders, and/or anxiety.

CRF-R1 Receptor Binding Assay for the Evaluation of Biological Activity

The following is a description of the isolation of cell membranes containing cloned human CRF-R1 receptors for use in the standard binding assay as well as a description of the assay itself.

Messenger RNA was isolated from human hippocampus. The mRNA was reverse transcribed using oligo (dt) 12-18 and the coding region was amplified by PCR from start to stop codons. The resulting PCR fragment was cloned into the EcoRV site of pGEMV, from whence the insert was reclaimed using XhoI + XbaI and cloned into the XhoI + XbaI sites of vector pm3ar (which contains a CMV promoter, the SV40 't' splice and early poly A signals, an Epstein-Barr viral origin of replication, and a hygromycin selectable marker). The resulting expression vector, called phchCRFR was transfected in 293EBNA cells and cells retaining the episome were selected in the presence of 400 μ M hygromycin. Cells surviving 4 weeks of selection in hygromycin were pooled, adapted to growth in suspension and used to generate membranes for the binding assay described below. Individual aliquots containing approximately 1×10^8 of the suspended cells were then centrifuged to form a pellet and frozen.

For the binding assay a frozen pellet described above containing 293EBNA cells transfected with hCRFR1 receptors is homogenized in 10 ml of ice cold tissue buffer (50 mM HEPES buffer pH 7.0, containing 10 mM $MgCl_2$, 2 mM EGTA, 1 μ g/ml aprotinin, 1 μ g/ml leupeptin and 1 μ g/ml pepstatin). The homogenate is centrifuged at 40,000 x g for 12 min and the resulting pellet rehomogenized in 10 ml of tissue buffer. After another centrifugation at 40,000 x g for 12 min, the

pellet is resuspended to a protein concentration of 360 µg/ml to be used in the assay.

Binding assays are performed in 96 well plates; each well having a 300 µl capacity. To each well is added 50 µl of test drug dilutions (final concentration of drugs range from 10^{-10} - 10^{-5} M), 100 µl of ^{125}I -ovine-CRF (^{125}I -o-CRF) (final concentration 150 pM) and 150 µl of the cell homogenate described above. Plates are then allowed to incubate at room temperature for 2 hours before filtering the incubate over GF/F filters (presoaked with 0.3% polyethyleneimine) using an appropriate cell harvester. Filters are rinsed 2 times with ice cold assay buffer before removing individual filters and assessing them for radioactivity on a gamma counter.

Curves of the inhibition of ^{125}I -o-CRF binding to cell membranes at various dilutions of test drug are analyzed by the iterative curve fitting program LIGAND [P.J. Munson and D. Rodbard, *Anal. Biochem.* 107:220 (1980)], which provides K_i values for inhibition which are then used to assess biological activity.

A compound is considered to be active if it has a K_i value of less than about 10000 nM for the inhibition of CRF.

Inhibition of CRF-Stimulated Adenylate Cyclase Activity

Inhibition of CRF-stimulated adenylate cyclase activity can be performed as described by G. Battaglia et al. *Synapse* 1:572 (1987). Briefly, assays are carried out at 37° C for 10 min in 200 ml of buffer containing 100 mM Tris-HCl (pH 7.4 at 37° C), 10 mM MgCl_2 , 0.4 mM EGTA, 0.1% BSA, 1 mM isobutylmethylxanthine (IBMX), 250 units/ml phosphocreatine kinase, 5 mM creatine phosphate, 100 mM guanosine 5'-triphosphate, 100 nM oCRF, antagonist peptides (concentration range 10^{-9} to 10^{-6}M) and 0.8 mg original wet weight tissue (approximately 40-60 mg protein). Reactions are initiated by the addition of 1 mM ATP/ ^{32}P ATP (approximately 2-4 mCi/tube) and terminated by the addition of 100 ml of 50 mM Tris-HCL, 45 mM ATP and 2% sodium dodecyl sulfate. In order to monitor the recovery of cAMP,

1 μ l of [3 H]cAMP (approximately 40,000 dpm) is added to
each tube prior to separation. The separation of [32 P]cAMP
from [32 P]ATP is performed by sequential elution over Dowex
and alumina columns.

5

In vivo Biological Assay

The *in vivo* activity of the compounds of the present
invention can be assessed using any one of the biological
assays available and accepted within the art. Illustrative
10 of these tests include the Acoustic Startle Assay, the
Stair Climbing Test, and the Chronic Administration Assay.
These and other models useful for the testing of compounds
of the present invention have been outlined in C.W.
Berridge and A.J. Dunn *Brain Research Reviews* 15:71 (1990).
15 Compounds may be tested in any species of rodent or small
mammal.

Dosage and Formulation

Compounds of this invention can be administered to
20 treat these abnormalities by means that produce contact of
the active agent with the agent's site of action in the
body of a mammal. The compounds can be administered by any
conventional means available for use in conjunction with
pharmaceuticals either as individual therapeutic agent or
25 in combination of therapeutic agents. They can be
administered alone, but will generally be administered with
a pharmaceutical carrier selected on the basis of the
chosen route of administration and standard pharmaceutical
practice.
30 The dosage administered will vary depending on the use
and known factors such as pharmacodynamic character of the
particular agent, and its mode and route of administration;
the recipient's age, weight, and health; nature and extent
of symptoms; kind of concurrent treatment; frequency of
35 treatment; and desired effect. For use in the treatment of
said diseases or conditions, the compounds of this
invention can be orally administered daily at a dosage of
the active ingredient of 0.002 to 200 mg/kg of body weight.

Ordinarily, a dose of 0.01 to 10 mg/kg in divided doses one to four times a day, or in sustained release formulation will be effective in obtaining the desired pharmacological effect.

5 Dosage forms (compositions) suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5 to 95% by weight based on
10 the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets and powders; or in liquid forms such as elixirs, syrups, and/or suspensions. The compounds of this invention can also be
15 administered parenterally in sterile liquid dose formulations.

Gelatin capsules can be used to contain the active ingredient and a suitable carrier such as but not limited to lactose, starch, magnesium stearate, steric acid, or
20 cellulose derivatives. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar-coated or film-coated to
25 mask any unpleasant taste, or used to protect the active ingredients from the atmosphere, or to allow selective disintegration of the tablet in the gastrointestinal tract.

Liquid dose forms for oral administration can contain coloring or flavoring agents to increase patient
30 acceptance.

In general, water, pharmaceutically acceptable oils, saline, aqueous dextrose (glucose), and related sugar solutions and glycols, such as propylene glycol or polyethylene glycol, are suitable carriers for parenteral
35 solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents, such as sodium

bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, are suitable stabilizing agents. Also used are citric acid and its salts, and EDTA. In addition, parenteral solutions can contain preservatives such as
5 benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences", A. Osol, a standard reference in the field.

10 Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

15 A large number of units capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg lactose, 50 mg cellulose, and 6 mg magnesium stearate.

20 Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean, cottonseed oil, or olive oil is prepared and injected by means of a positive displacement was pumped into gelatin to form soft gelatin capsules containing 100
25 mg of the active ingredient. The capsules were washed and dried.

Tablets

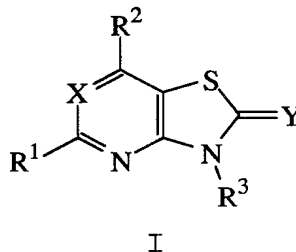
A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg active
30 ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg lactose. Appropriate coatings may be applied to increase palatability or delayed adsorption.

35 The compounds of this invention may also be used as reagents or standards in the biochemical study of neurological function, dysfunction, and disease.

Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced
5 otherwise that as specifically described herein.

**WHAT IS CLAIMED AS NEW AND DESIRED TO BE SECURED BY
LETTER PATENT OF UNITED STATES IS:**

1. A compound of formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

X is CR⁴ or N;

Y is selected from the group: S, O and NR⁵;

R¹ is selected from the group: H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, Cl, F, Br, I, -CN, C₁₋₅ haloalkyl, -NR⁶R⁷, -NR⁶COR⁷, -OR⁸, -SH, and -S(O)_nR⁹;

n is independently at each occurrence selected from the group: 0, 1, and 2;

R² is selected from the group: -CR¹⁰R¹¹R¹², -NR^{10a}R^{11a}, -NHCR¹⁰R¹¹R¹², -OCR¹⁰R¹¹R¹², and phenyl, wherein the phenyl is substituted with 0-4 R^a;

R^a is independently at each occurrence selected from the group: Cl, F, Br, I, C₁₋₄ haloalkyl, -NO₂, C₁₋₄ alkyl, C₂₋₅ alkenyl, C₂₋₄ alkynyl, C₃₋₇ cycloalkyl, C₂₋₅ carboalkoxy, SH, -S(C₁₋₄ alkyl), -CN, -OH, C₁₋₄ alkoxy, and -NR⁶R⁷, OR⁸, COR⁷;

R³ is selected from the group: phenyl, pyridyl, pyrimidyl, naphthyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, thiazolyl, pyrrolyl, oxazolyl, benzofuranyl,

benzothienyl, benzothiazolyl, isoxazolyl, and pyrazolyl,
and is substituted with 1 to 4 R^b groups;

5 R^b is independently at each occurrence selected from the
group: C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆
cycloalkyl, (C₃₋₈ cycloalkyl)C₁₋₄ alkyl-, NO₂, Cl, F,
Br, I, -CN, C₁₋₆ haloalkyl, -NR¹⁴R¹⁵, -NR⁸COR¹⁴, -
NR⁸CO₂R¹⁴, -COR¹⁴, -OR¹⁴, -CONR¹⁴R¹⁵, -CO₂R¹⁴, -SH, and -
S(O)_nR¹⁴;

10 R⁴ is selected from the group: H, C₁₋₄ alkyl, and C₁₋₄
haloalkyl, halogen, NH₂, NH(C₁₋₄ alkyl), NH(C₁₋₄ alkyl)₂,
CN, OR⁸;

15 R⁵ is -CO(C₁₋₄ alkyl) or -CO₂(C₁₋₄ alkyl);

R⁶ and R⁷ independently at each occurrence selected from the
group: H, C₁₋₄ alkyl, and C₃₋₆ cycloalkyl;

20 R⁸ is independently at each occurrence selected from the
group: H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, and C₃₋₆
cycloalkyl;

25 R⁹ is independently at each occurrence selected from the
group: C₁₋₄ alkyl, C₁₋₄ haloalkyl, and aryl;

30 R¹⁰ and R¹¹ are independently at each occurrence selected from
the group: C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈
cycloalkyl, (C₃₋₈ cycloalkyl)C₁₋₄ alkyl-, -(CH₂)_naryl, -
(CH₂)_nheteroaryl, (C₁₋₆ alkoxy)C₁₋₆ alkyl-, -C₀₋₆-CN, -
NH(C₁₋₆ alkyl), -N(C₁₋₆ alkyl)₂, and (carbo-C₁₋₆ alkoxy)
C₀₋₆ alkyl-, each R¹⁰ and R¹¹ being optionally substituted
with 0-3 R^c;

35 R^c is independently at each occurrence selected from the
group: F, =O, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₂₋₄ alkenyl,
C₂₋₄ alkynyl, C₁₋₄ alkoxy, -CN, S(O)_nC₁₋₄ alkyl, NH₂,

NH(C₁₋₄ alkyl), N(C₁₋₄ alkyl)₂, phenyl, pyridyl, and pyrimidyl;

5 R¹² is independently at each occurrence selected from the group: H, C₁₋₆ alkyl;

alternatively, R¹⁰ and R¹¹ are taken together, along with the interconnected carbon, to form a 4-8 membered saturated or partially saturated carbocyclic ring substituted with
10 0-2 R^e or a 4-8 membered saturated or partially saturated heterocyclic ring containing 1-2 heteroatoms selected from O, N, NR⁸, and S and substituted with 0-2 R^d;

15 R^d is independently at each occurrence selected from the group: =O, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxy, -CN, -S(O)_nC₁₋₄ alkyl, -NH₂, -NH(C₁₋₄ alkyl), -N(C₁₋₄ alkyl)₂, and phenyl;

20 R^{10a} and R^{11a} are independently at each occurrence selected from the group: C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, (C₃₋₈ cycloalkyl)C₁₋₄ alkyl-, -(CH₂)_naryl, -(CH₂)_nheteroaryl, (C₁₋₆ alkoxy)C₁₋₆ alkyl-, -C₁₋₆-CN, -NH(C₁₋₆ alkyl), -N(C₁₋₆ alkyl)₂, (carbo-C₁₋₆ alkoxy)C₁₋₆ alkyl-, S(O)_nR⁸, C(O)₁₋₂R⁸, and C(O)NR⁶R⁷ each R^{10a} being substituted with
25 0-3 R^c;

alternatively, R^{10a} and R^{11a} are taken together, along with the interconnected nitrogen, to form a 4-8 membered saturated or partially saturated heterocyclic ring containing 0-1
30 additional heteroatoms selected from O, N, NR⁸, and S and substituted with 0-3 R^e;

R¹⁴ and R¹⁵ are independently at each occurrence selected from the group: H, C_{1-C4} alkyl, C_{1-C4} haloalkyl, C_{3-C6}
35 cycloalkyl, (C₃₋₈ cycloalkyl)C₁₋₄ alkyl-, aryl, -(C_{1-C4} alkyl)aryl, heteroaryl and -(C_{1-C4})heteroaryl;

aryl is phenyl substituted with 0-3 R^e;

R^e is independently selected at each occurrence from the group: C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-5} alkynyl, C_{3-6} cycloalkyl, $-NO_2$, Cl, F, Br, I, $-CN$, C_{1-4} haloalkyl, $-NH_2$,
5 $-NH(C_{1-4} \text{ alkyl})$, $-N(C_{1-4} \text{ alkyl})_2$, OR^{14} , $S(O)_nR^{14}$; and,

heteroaryl is independently at each occurrence selected from the group: pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl,
10 thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl and pyrazolyl substituted with 0-3 R^f .

2. A compound according to Claim 1, wherein:

15 Y is S or O;

R^1 is selected from the group: H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, Cl, F, $-CN$, C_{1-5} haloalkyl, and $-NR^6R^7$;

20 R^3 is selected from the group: phenyl, pyridyl, and pyrimidyl, and is substituted with 1 to 4 R^b groups;

25 R^b is independently at each occurrence selected from the group: C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-6} cycloalkyl, $(C_{3-8} \text{ cycloalkyl})C_{1-4} \text{ alkyl-}$, NO_2 , Cl, F, $-CN$, C_{1-4} haloalkyl, $-NR^{14}R^{15}$, $-NR^8COR^{14}$, $-NR^8CO_2R^{14}$, $-COR^{14}$, $-OR^{14}$, $-CONR^{14}R^{15}$, $-CO_2R^{14}$, $-SH$, and $-S(O)_nR^{14}$;

30 heteroaryl is independently at each occurrence selected from the group: pyridyl, pyrimidinyl, triazinyl, furanyl, thienyl, imidazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, isoxazolyl and pyrazolyl substituted with 0-3 R^e .

35 3. A compound according to Claim 1, wherein the compound is selected from the group:

3-(2-Bromo-4-isopropyl)phenyl-5-methyl-7-morpholino-
thiazolo[4,5-d]pyrimidin-2-thione;

5 3-(2-Bromo-4-isopropyl)phenyl-7-(N-cyclopropylmethyl-N-
propyl)amino-5-methylthiazolo[4,5-d]pyrimidin-2-thione;

3-(2-Bromo-4-isopropyl)phenyl-7-(N,N-diethylamino)-5-methyl-
thiazolo[4,5-d]pyrimidin-2-thione;

10 7-(N,N-bismethoxyethylamino)-3-(2-bromo-4-isopropyl)phenyl-5-
methylthiazolo[4,5-d]pyrimidin-2-thione;

3-(2-Bromo-4-isopropyl)phenyl-7-(N-butyl-N-ethyl)amino-5-
methylthiazolo[4,5-d]pyrimidin-2-thione;

15 3-(2-Bromo-4-isopropyl)phenyl-7-(N,N-di-sec-butylamine)-5-
methylthiazolo[4,5-d]pyrimidin-2-thione;

20 7-(N,N-diethylamino)-5-methyl-3-(2,4,6-
trimethyl)phenylthiazolo[4,5-d]pyrimidin-2-thione;

7-(N,N-bismethoxyethylamino)-5-methyl-3-(2,4,6-
trimethyl)phenylthiazolo[4,5-d]pyrimidin-2-thione;

25 7-(N-cyclopropylmethyl-N-propyl)-5-methyl-3-(2,4,6-
trimethyl)phenylthiazole[4,5-d]pyrimidin-2-thione;

3-(2-Bromo-4-isopropyl)phenyl-7-(N-cyclopropylmethyl-N-
propyl)amino-5-methylthiazolo[4,5-d]pyrimidin-2-one;

30 7-(N,N-bismethoxyethylamino)-3-(2-bromo-4-isopropyl)phenyl-5-
methylthiazolo[4,5-d]pyrimidin-2-one;

35 3-(2-Bromo-4-isopropyl)phenyl-7-(N,N-diethylamino)-5-
methylthiazolo[4,5-d]pyrimidin-2-one;

7-(N,N-diethylamino)-5-methyl-3-(2,4,6-
trimethyl)phenylthiazolo[4,5-d]pyrimidin-2-one;

7- (N,N-bismethoxyethylamino)-5-methyl-3-(2,4,6-trimethyl)phenylthiazolo[4,5-d]pyrimidin-2-one; and,

5 7- (N-cyclopropylmethyl-N-propyl) amino-5-methyl-3-(2,4,6-trimethyl)phenylthiazolo[4,5-d]pyrimidin-2-one;

or a pharmaceutically acceptable salt form thereof.

10

4. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to Claim 1, or a pharmaceutically acceptable salt form thereof.

15

5. A method of treating psychiatric disorders and neurological diseases including affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, in a mammal, comprising:

20 stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems,

25 human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, in a mammal, comprising:

30 administering to the mammal a therapeutically effective amount of a compound of Claim 1 or a pharmaceutically acceptable salt form thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/06825

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D513/04 A61K31/505 A61K31/44 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | <p>TIWARI N ET AL: "Synthesis and fungicidal activity of some 3,7-diaryl-6-cyanorhodanino-4,5-bispyridin-5(4H)-ones and 3-aryl-rhodanino-4,5-bisfuran-6(5H)-ones" INDIAN J. CHEM., SECT. B, vol. 28B, no. 9, 1989, pages 796-798, XP002110163 page 796; scheme 1, the compounds IVa - IVc, IVe and IVf</p> <p style="text-align: center;">--- -/--</p> | 1 |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

- 26 July 1999

Date of mailing of the international search report

18.08.99

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/06825

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | <p>SINGH A ET AL: "Studies in 4-aminothiazolines: Part XVI. Synthesis of thiazolo'4,5-d!pyrimidines and related systems and reactions of functionalized primary amines with 5-cyano-4-ethoxymethyleneamino-4-t hiazolines"</p> <p>INDIAN J. CHEM., SECT. B , vol. 19B, no. 1, 1980, pages 37-41, XP002110164 page 37; scheme 1, the compound VII wherein R = o-tolyl and R = allyl (see also page 40; column 2, the fourth paragraph)</p> <p style="text-align: center;">---</p> | 1 |
| X | <p>SINGH A ET AL: "Synthesis of thiazolo'4,5-d!pyrimidines;a new class of CNS depressants. Studies in 4-aminothiazolines. XIII"</p> <p>J. INDIAN CHEM. SOC., vol. 55, no. 10, 1978, pages 1040-1042, XP002110165 page 1040; scheme 1, the compound VII wherein R1 = n-propyl and R = o-tolyl or p-tolyl (see also page 1041; table 1, the compounds no. 6 and 7)</p> <p style="text-align: center;">---</p> | 1 |
| X | <p>WO 98 08847 A (PFIZER ;CHEN YUHPYNG LIANG (US)) 5 March 1998 (1998-03-05) page 50 - page 52; claim 1 see page 6; formula I-K page 1, line 11 - line 12</p> <p style="text-align: center;">---</p> | 1-5 |
| A | <p>WO 95 33750 A (PFIZER ;CHEN YUHPYNG L (US)) 14 December 1995 (1995-12-14) page 72 - page 74; claim 1 page 77; claim 13 page 35 - page 36; example 9 page 62; examples 108,110</p> <p style="text-align: center;">---</p> | 1-5 |
| A | <p>CHRISTOS T E ET AL: "Corticotrophin-releasing factor receptor antagonists"</p> <p>EXPERT OPIN. THER. PAT., vol. 8, no. 2, February 1998 (1998-02), pages 143-152, XP002110166 the whole document</p> <p style="text-align: center;">-----</p> | 1-5 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/06825

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 5 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. l. Application No

PCT/US 99/06825

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| WO 9533750 A | 14-12-1995 | AU 692548 B AU 2453095 A BR 9502708 A CA 2192354 A CN 1150428 A EP 0764166 A FI 964894 A HR 950321 A HU 75774 A JP 9507249 T NO 965237 A NZ 285442 A PL 320631 A ZA 9504677 A | 11-06-1998 04-01-1996 30-04-1996 14-12-1995 21-05-1997 26-03-1997 05-12-1996 28-02-1998 28-05-1997 22-07-1997 06-02-1997 27-05-1998 13-10-1997 09-12-1996 |